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Effect of transoral incisionless fundoplication on reflux mechanisms

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Abstract

Objectives Transoral incisionless fundoplication (TIF) is a new endoscopic treatment option for gastroesophageal reflux disease (GERD). The mechanisms underlying the anti-reflux effect of this new procedure have not been studied. We therefore conducted this explorative study to evaluate the effect of TIF on reflux mechanisms, focusing on transient lower esophageal sphincter relaxations (TLESRs) and esophagogastric junction (EGJ) distensibility.

Methods GERD patients ($N = 15$; 11 males, mean age 41 years, range 23–66), dissatisfied with medical treatment were studied before and 6 months after TIF. We performed 90-min postprandial combined high-resolution manometry and impedance-pH monitoring and an ambulatory 24-h pH-impedance monitoring. EGJ distensibility was evaluated using an endoscopic functional luminal imaging probe before and directly after the procedure.

Results TIF reduced the number of postprandial TLESRs (16.8 ± 1.5 vs. 9.2 ± 1.3; $p < 0.01$) and the number of postprandial TLESRs associated with reflux (11.1 ± 1.6 vs. 5.6 ± 0.6; $p < 0.01$), but the proportion of TLESRs associated with reflux was unaltered (67.6 ± 6.9 vs. 69.9 ± 6.3 %). TIF also led to a decrease in the number and proximal extent of reflux episodes and an improvement of acid exposure in the upright position; conversely, TIF had no effect on the number of gas reflux episodes. EGJ distensibility was reduced after the procedure (2.4 ± 0.3 vs. 1.6 ± 0.2 mm^2/mmHg; $p < 0.05$).

Conclusions TIF reduced the number of postprandial TLESRs, the number of TLESRs associated with reflux and EGJ distensibility. This resulted in a reduction of the number and proximal extent of reflux episodes and improvement of acid exposure in the upright position. The anti-reflux effect of TIF showed to be selective for liquid-containing reflux only, thereby preserving the ability of venting gastric air.

Keywords Gastro-esophageal reflux disease (GERD) · Transoral incisionless fundoplication (TIF) · Transient lower esophageal sphincter relaxations (TLESRs) · High-resolution manometry (HRM) · Esophagogastric junction (EGJ) distensibility

In the past decade, new endoscopic approaches for the treatment of gastroesophageal reflux disease (GERD) have been introduced to fill the therapeutic gap between treatment with proton pump inhibitors (PPIs) and laparoscopic anti-reflux surgery (LARS). To date, most of these endoscopic techniques have failed, either because of a lack of long-term efficacy or due to complications of the procedure [1–4]. Transoral incisionless fundoplication (TIF) using the EsophyX device is a recently developed endoscopic treatment option for GERD. In this procedure, a partial fundoplication is created under general anesthesia by sequential retractions of tissue, fixed by multiple transmurally placed polypropylene fasteners [5]. Since its first introduction, several modifications have been made to the EsophyX device and to

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the TIF procedure. Using the TIF 1.0 technique, a neo-gastroesophageal valve was created by gastro-gastric plication, but modifications of fastener deployment led to a longer valve constructed by esophagogastric plication (TIF 2.0 technique) [6, 7]. Uncontrolled clinical trials reported promising results, with respect to both symptom scores and PPI use, as well as in objective reflux parameters [8–11]. The introduction of the TIF 2.0 technique and the extensive experience of the operating team have led to improved results in our medical center. A randomized controlled trial comparing TIF with PPI therapy was initiated, and long-term follow-up data from this trial are awaited; in the context of this trial, we performed the present study, to assess the effect of TIF 2.0 on reflux mechanisms.

Several studies investigating the effect of LARS on reflux mechanisms have shown a reduction in both the number of transient lower esophageal sphincter relaxations (TLESRs) as well as the proportion of TLESRs associated with reflux [12, 13]. TLESRs have been identified as the predominant mechanism for reflux to occur in both healthy subjects and GERD patients [14–17]. A reduction in the number of TLESRs after LARS is considered to contribute to the anti-reflux effect of the procedure. The proportion of TLESRs associated with reflux is higher in GERD patients than in healthy subjects, while the total number of TLESRs is in the same range in both groups [18, 19]. This difference in TLESRs associated with reflux may be explained by an increased distensibility of the esophagogastric junction (EGJ): under the same distending pressure, the EGJ opens to a greater extent in GERD patients, allowing gastric contents to reflux into the esophagus more easily [20]. This observation has recently been confirmed employing a new technique designed to measure intraluminal distensibility with the endoscopic functional luminal imaging probe (EndoFLIP) [21]. We aimed to investigate the mechanisms underlying the anti-reflux effect of TIF in this first explorative study, focusing on the effect of TIF on TLESRs, TLESRs associated with reflux, and EGJ distensibility.

Methods

Study population

From 2008 to 2012, TIF was performed in 60 GERD patients who were enrolled in a prospective trial evaluating the TIF procedure at the Maastricht University Medical Centre. Throughout this period, 15 of these patients [11 males, mean age 41 years (range 23–66), mean body mass index 26.2 ± 1.1 kg/m^2] agreed to participate in the present study investigating the effect of TIF on reflux mechanisms.

All patients had chronic (>6 months) GERD symptoms, such as heartburn, regurgitation, or retrosternal pain and were offered TIF as they were dissatisfied with PPI treatment or unwilling to undergo life-long PPI therapy. GERD was well documented by upper gastrointestinal (GI) endoscopy and 24-h impedance-pH monitoring, showing esophagitis and/or pathologic acid exposure time (pH below 4 for >4.0 % of time) with a high (≥95 %) symptom association probability (SAP) [22]. Of the 15 patients, 8 (53 %) had documented reflux esophagitis on baseline endoscopy; three had a grade A esophagitis, four had grade B, and one had grade C (LA classification). Preoperative endoscopy showed a small (≤2 cm) hiatal hernia in nine patients. Additionally, the gastroesophageal flap valve grade according to the Hill classification was assessed in all patients: grade 1 was found in one patient, grade 2 in seven patients, grade 3 in five patients, and grade 4 in two patients [23].

Exclusion criteria were as follows: patients <18 years of age, severe esophageal motility disorder on manometry, hiatal hernia >2 cm in length, a history of previous anti-reflux surgery, reflux esophagitis grade D (LA classification), Barrett's epithelium, esophageal stricture or ulcer, current pregnancy, or severe comorbidities (including cardiopulmonary disease, portal hypertension, coagulation disorders, immunosuppression, or morbid obesity). The protocol was approved by the Medical Ethical Committee of the Maastricht University Medical Center (9 June 2008), and written informed consent was obtained from all patients.

Study protocol

Patients were studied before and 6 months after the TIF procedure. A test day consisted of two parts as shown in (Fig. 1). During the first part of 90 min, postprandial measurements were performed using combined stationary high-resolution manometry (HRM) and impedance-pH monitoring. The second part consisted of 24-h ambulatory impedance-pH monitoring. For at least 5 days before testing, the use of anti-secretory drugs or drugs that influence gastroesophageal motility was ceased. After an overnight fast, both the manometric and impedance-pH catheters were introduced transnasally. End expiratory (LES) resting pressure was determined shortly before patients consumed a standardized high-caloric (960 kCal) liquid meal consisting of Nutridrink Juice Style [400 ml, containing 16 g protein, 134 g carbohydrates (pH 2.9)] and Nutricia Calogen [80 ml, containing 80 g fat (pH 5.6)] (Nutricia, Zoetermeer, the Netherlands) within 15 min. Subsequently, impedance-pH and HRM recordings were started simultaneously and were continued for 90 min. During this period, patients were in an upright position and were not allowed to doze. The 24-h impedance-pH monitoring was started after the HRM catheter was removed.

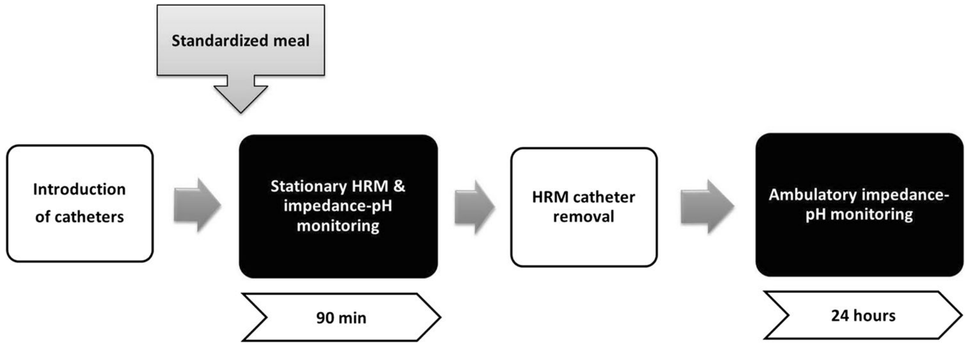

Fig. 1 Flow chart of the study protocol. *HRM* high-resolution manometry

Combined stationary high-resolution manometry and impedance-pH monitoring

A solid-state HRM catheter (Unisensor AG, Attikon, Switzerland) was used, containing 36 pressure sensors spaced at a 1-cm interval and a maximum outer diameter of 5.3 mm. Catheter position was considered correct when both the upper esophageal sphincter (UES) and LES were visible and at least two sensors were located in the stomach. Color contour plots were displayed directly and saved at the end of the study. A combined impedance-pH catheter (Unisensor AG, Attikon, Switzerland) was positioned alongside the HRM catheter. The catheter contained six impedance segments and one ISFET pH electrode. The recording segments were located at 2–4, 4–6, 6–8, 8–10, 14–16, and 16–18 cm above the upper border of the LES. The pH-electrode was positioned 5 cm above the upper border of the LES, according to the manometric color plot. Impedance and pH signals were stored in a digital data logger (Ohmega, Medical Measurement Systems, Enschede, The Netherlands). After 90 minutes of recording, the HRM catheter was removed.

Ambulatory 24-h impedance-pH monitoring

The impedance-pH catheter, left in situ, was used for the 24-h ambulatory monitoring. Patients were instructed to continue their regular diet, to report GERD symptoms and to keep a diary of their consumption and body position (supine or upright) during the ambulatory measurement.

Transoral incisionless fundoplication

TIF using the EsophyX-2 device (EndoGastric solutions, Inc., Redmond, WA, USA) has previously been described in detail [24]. In short, the procedure was performed under general endotracheal anesthesia by a team comprising a surgeon and a gastroenterologist. After transoral introduction of the device, the endoscope was positioned in retroflexion for optimal visualization. A built-in vacuum invaginator was used to reposition the squamocolumnar junction below the diaphragm in case of a hiatal hernia.

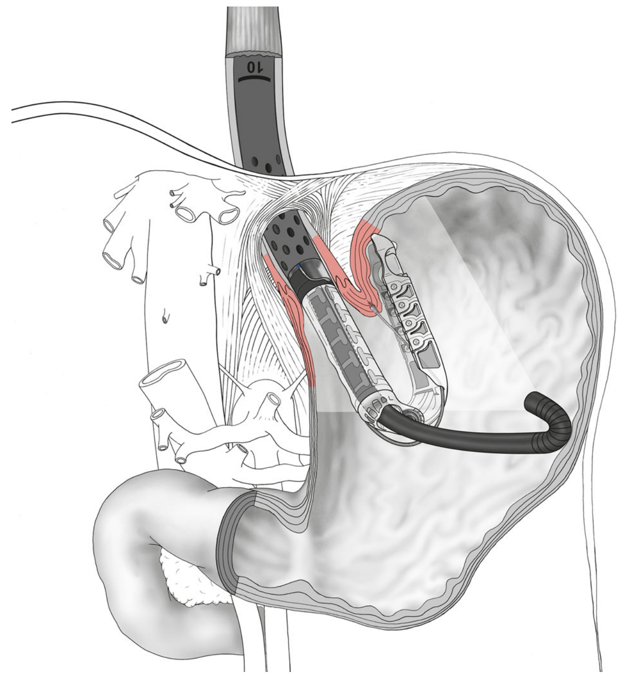

Fig. 2 Illustration of transoral incisionless fundoplication with a depiction of the EsophyX device, including the helical retractor inserted into the Z-line

Subsequently, a tissue mold within the device was retroflexed and a helical retractor was inserted into the Z-line (Fig. 2). With caudal retraction on the retractor, the tissue mold was used to rotate the fundus up and around the esophagus and circumferential deployment of multiple fasteners ensured a fixed neogastro-esophageal valve. The procedures were carried out by a single surgeon (N.B.) and gastroenterologist (J.M.C.) at the Maastricht University Medical Center.

Assessment of esophagogastric junction distensibility (EGJ) using EndoFLIP

An endoscopic functional luminal imaging probe, EndoFLIP (Crospon Ltd, Galway, Ireland), was used to assess EGJ distensibility, according to previously described concepts [21, 25]. In short, the EndoFLIP measurement system uses impedance planimetry to assess multiple cross-sectional areas (CSAs) within a cylindrical bag placed over the EGJ. With simultaneous pressure measurements within the cylindrical bag, the distensibility (CSA/pressure response) over the EGJ can be assessed. During the procedure, shortly before introduction of the EsophyX device, the EndoFLIP probe was placed at the level of the EGJ according to previous endoscopic inspection. The bag was filled to 30 ml, as this volume appears to be the most relevant distension level [26, 27]. Corresponding CSA and distension pressure measurements were performed. EndoFLIP measurements were monitored in real time to ensure the correct location of the bag. In case of migration of the bag, the measurements were repeated after repositioning the bag. Directly after removal of the EsophyX device and the final endoscopic inspection, the EndoFLIP measurements were repeated while patients were still under general anesthesia.

Assessment of symptoms and medication use

Pre- and postoperative symptoms were assessed using a disease-specific quality-of-life questionnaire (GERD-HRQL) [28, 29]. The GERD-HRQL questionnaire assesses reflux-related symptoms using a scale of 0 (no symptoms) to 5 (incapacitating). The maximum score for the GERD-HRQL is 50 points. Preoperative use of acid-suppressive drugs was assessed at the outpatient clinic and again at 6 months follow-up.

Data analysis

Analysis of the postprandial HRM measurements was carried out by a single investigator, who was blinded for the pre- or postoperative status of the patient. End expiratory LES pressure was determined before consumption of the liquid meal and referenced to end expiratory intragastric pressure. TLESRs were visually detected and scored with the color contour plot, using the criteria developed by Holloway et al. [30] and later modified for HRM [31]. Postprandial impedance-pH tracings were manually analyzed independent of the manometric findings by the same investigator. The analysis of the impedance-pH monitoring included the number of reflux episodes, composition (liquid, gas, and mixed), proximal extent, and acidity of the refluxate. According to previously described definitions [32], liquid reflux was defined as a fall >50 % in impedance compared with the baseline impedance level, beginning at the most distal recording site and reaching at least the next two proximal measuring segments. Gas reflux was defined as a sharp (>3,000 Ohms) rise in impedance that moved in a retrograde direction beginning at the most distal recording site and reaching at least the next two proximal measuring segments. Mixed reflux was defined as gas reflux occurring during or immediately preceding liquid reflux. Mixed and pure liquid reflux episodes were grouped as liquid-containing reflux episodes for further analysis of the underlying mechanisms. Using the pH tracings, reflux episodes were classified as acid reflux when the nadir $pH < 4$, or non-acidic reflux when $pH \geq 4$. Reflux episodes were classified as proximal (reaching ≥17 cm above the LES), mid-esophageal (7–17 cm above the LES) or distal (≤7 cm).

Data from postprandial HRM and impedance-pH monitoring were combined, analyzing the occurrence of liquid-containing reflux and simultaneous TLESR or other mechanisms underlying the reflux episode. Mechanisms of liquid-containing reflux were classified as TLESR induced, swallow induced, abdominal straining induced, or due to absent/low basal LES pressure [17, 33]. In case of liquid-containing reflux episodes during movement-induced artefacts, the mechanism was defined as non-interpretable. The ambulatory 24-h impedance-pH measurements were manually analyzed in the same manner as the postprandial measurements, excluding the periods of meal consumption.

Analysis of the EndoFLIP measurements to assess the EGJ distensibility was based on the narrowest CSA and the corresponding intrabag pressure. CSA and intrabag pressure were assessed by quantifying the 50th percentile of each recording of 30 s. EGJ distensibility was calculated as the narrowest CSA in mm^2/intrabag pressure in mmHg.

Statistical analysis

All data are shown as mean ± standard error of the mean (SEM), unless stated otherwise. Data were checked for normality using the Kolmogorov–Smirnov test. Comparisons between pre-operative and postoperative measurements were performed using the Wilcoxon signed rank test for non-parametric data and paired *t*-test for parametric data. The significance level was set at $p < 0.05$. All statistical analyses were performed using commercially available computer software (PASW Statistics 18 for Windows, © SPSS, Inc., 2009, Chicago, IL, USA).

Results

Stationary esophageal manometry and impedance-pH monitoring (90 min)

TIF resulted in a marked reduction of both the number of TLESRs (from 16.8 ± 1.5 to 9.2 ± 1.3; $p < 0.01$) and the number of TLESRs associated with liquid-containing reflux after the procedure (from 11.1 ± 1.6 to 5.6 ± 0.6;

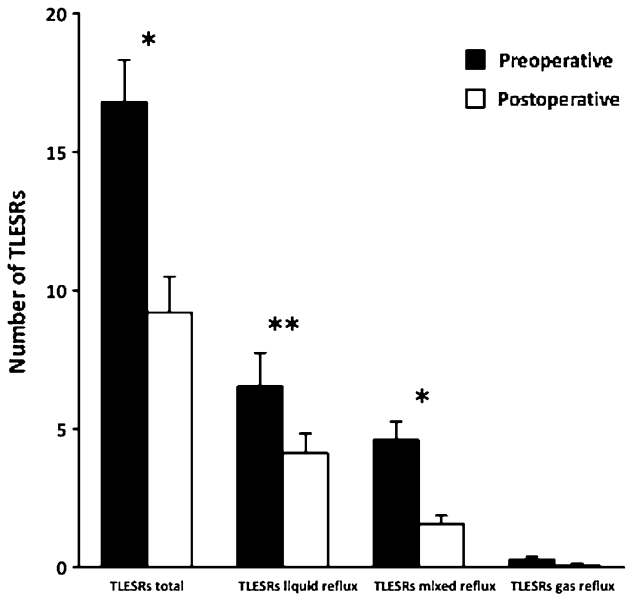

Fig. 3 Number of transient lower esophageal sphincter relaxations (TLESRs) before and after transoral incisionless fundoplication during the 90-min postprandial period. $*p < 0.01$, $**p < 0.05$

Table 1 Results of the combined high-resolution manometry and impedance-pH measurements during the 90 min postprandial period before and after transoral incisionless fundoplication

	Preoperative	Postoperative	*p* value
Total number of TLESRs	16.8 ± 1.5	9.2 ± 1.3	<0.01
TLESRs with liquid reflux	6.5 ± 1.2	4.1 ± 0.7	<0.05
TLESRs with mixed reflux	4.6 ± 0.7	1.6 ± 0.3	<0.01
TLESRs with gas reflux	0.3 ± 0.1	0.1 ± 0.1	NS
TLESRs with reflux (%)	67.6 ± 6.9	69.9 ± 6.3	NS
Total reflux episodes	18.8 ± 2.1	9.5 ± 1.6	<0.01
Liquid reflux episodes	9.7 ± 1.5	6.0 ± 1.2	<0.05
Mixed reflux episodes	7.6 ± 0.8	2.5 ± 0.5	<0.01
Gas reflux episodes	1.5 ± 0.4	1.0 ± 0.4	NS

NS not significant, *TLESR* transient lower esophageal sphincter relaxation

$p < 0.01$) (Fig. 3). Although the number of TLESRs with liquid-containing reflux episodes decreased, the proportion of TLESRs associated with liquid-containing reflux was not influenced by the procedure (from 67.6 ± 6.9 to 69.9 ± 6.3 %; $p = 0.80$) (Table 1).

Postprandial liquid containing reflux episodes were reduced after the procedure (from 18.8 ± 2.1 to 9.5 ± 1.6; $p < 0.01$), but TIF had no impact on the number of postprandial gas reflux episodes (Table 1). When determining the mechanism behind each liquid-containing reflux episode, TLESR was shown to be the dominant mechanism for reflux to occur, both before (63.5 %) and after TIF (68.1 %) (Table 2). The number of liquid-containing reflux episodes induced by TLESRs decreased after the procedure (from 10.1 ± 1.6 to 5.4 ± 0.7; $p < 0.01$), but the proportion of liquid-containing reflux episodes induced by a TLESR was unaltered. The number of liquid-containing reflux episodes induced by a swallow or by other mechanisms was not significantly altered by the procedure (Table 2). Basal LES pressure in the fasted state was increased after the procedure (from 13.9 ± 1.0 to 20.5 ± 1.8 mmHg; $p < 0.01$).

Table 2 Mechanisms underlying liquid containing reflux episodes of 15 patients with gastroesophageal reflux disease during 90-min postprandial period before and after transoral incisionless fundoplication

	Preoperative (%)	Postoperative (%)	*p* value
TLESR induced	165 (63.5)	81 (68.1)	<0.01
Swallow induced	65 (25.0)	29 (24.4)	NS
Abdominal straining	11 (4.2)	2 (1.7)	<0.05
Low LES pressure	13 (5.0)	5 (4.2)	NS
Non-interpretable	6 (2.3)	2 (1.7)	NS
Total reflux episodes	260 (100)	119 (100)	<0.001

LES lower esophageal sphincter, *NS* not significant, *TLESR* transient lower esophageal sphincter relaxations

Table 3 Results of the 24-h ambulatory impedance-pH measurements before and after transoral incisionless fundoplication

	Preoperative	Postoperative	*p* value
Total reflux episodes	124.0 ± 11.4	104.4 ± 13.7	0.06
Liquid reflux episodes	30.4 ± 3.5	16.7 ± 3.5	<0.01
Mixed reflux episodes	57.7 ± 5.7	45.1 ± 6.1	NS
Gas reflux episodes	35.9 ± .7.6	42.6 ± 10.2	NS
Proximal reflux episodes	36.7 ± 6.8	15.3 ± 2.9	<0.05
Proximal reflux episodes (%)	39.6 ± 4.9	24.6 ± 3.6	<0.05
Total acid exposure time (pH < 4) (%)	10.9 ± 1.9	7.3 ± 1.6	0.07
Upright acid exposure time (%)	11.7 ± 2.3	6.6 ± 1.0	<0.05
Supine acid exposure time (%)	10.2 ± 2.5	8.4 ± 3.0	NS

NS not significant

Ambulatory 24-h impedance-pH study

Mean esophageal acid exposure time was not significantly reduced (from 10.9 ± 1.9 to 7.3 ± 1.6 %; $p = 0.07$) 6 months after TIF. However, in the upright position, a significant reduction was observed (Table 3). TIF resulted in normalization of the esophageal acid exposure time (pH <4 for <4.0 % of time) in 47 % (7/15) of the patients. The esophageal acid exposure time of an additional 27 % (4/15) of the patients improved after the procedure. No differences in reflux mechanisms or EGJ characteristics were observed between patients with and without improved acid exposure time.

Analysis of 24-h impedance-pH tracings revealed a reduction in the number of liquid-containing reflux episodes after fundoplication (from 88.1 ± 6.1 to 61.8 ± 7.0; $p < 0.05$). The number of gas reflux episodes was not affected by the procedure (Table 3). The number and the percentage of proximal reflux episodes significantly decreased ($p < 0.05$). Furthermore, the percentage of acid reflux episodes with duration longer than 5 min decreased significantly (from 5.0 ± 1.2 to 2.3 ± 0.6; $p < 0.05$).

EGJ distensibility

Correct placement of the EndoFLIP probe was achieved in all patients, as indicated by the hourglass shape of the probe during insufflation. Mean distending pressure within the EndoFLIP bag during 30 ml distension was significantly higher after TIF (from 18.5 ± 1.6 to 21.8 ± 1.8 mmHg; $p < 0.05$), whereas hiatal CSA was not reduced (from 40.6 ± 5.4 to 33.6 ± 4.1 mm^2; $p = 0.27$). The mean EGJ distensibility (intrabag pressure/CSA) was significantly reduced after TIF (from 2.4 ± 0.3 to 1.6 ± 0.2 mm^2/mmHg; $p < 0.05$).

Clinical assessment

TIF reduced the GERD-HRQL score for heartburn (from 27.5 ± 1.8 to 13.2 ± 2.4; $p < 0.01$) (Fig. 4). Symptomatic remission was achieved in 12 patients (80 %) after TIF, eight of whom also showed a reduction in acid exposure time. Three patients (20 %) reported persistent daily GERD symptoms after the procedure, although acid exposure time was reduced below the normal range in two of these patients (pH <4 for <4.0 %) and by >50 % in the third patient. All three patients still showed a positive SAP ability on pH-impedance monitoring after the procedure. No differences were observed in the number of TLESRs, the number of reflux episodes or EGJ-characteristics that could account for the persistent symptoms after TIF.

None of the patients reported new symptoms of gas bloating or dysphagia after the procedure.

All patients were receiving a daily dosage of PPIs before the procedure. Ten of the 15 (67 %) patients reported complete cessation of anti-secretory medication at 6 months after the procedure. One patient used antacids daily for mild symptoms, and four patients (27 %) continued PPI use because of persistent symptoms after the procedure. However,

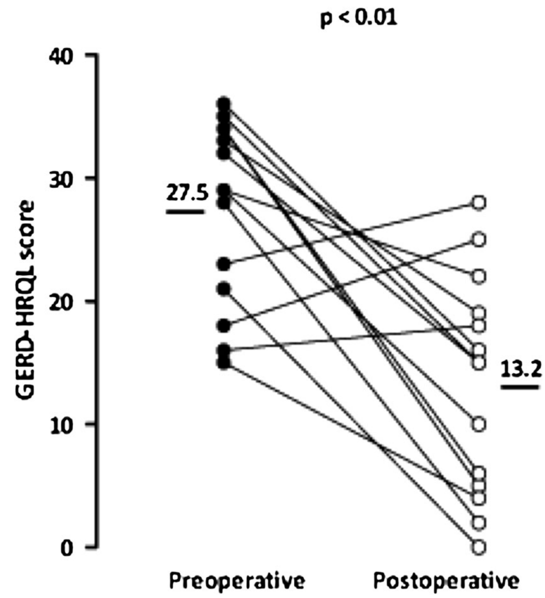

Fig. 4 GERD-HRQL scores for each individual patient before (*closed circles*) and 6 months after (*open circles*) transoral incisionless fundoplication. *Horizontal bars* indicate mean values. *GERD-HRQL* gastroesophageal reflux disease-specific health-related quality-of-life questionnaire

three of those patients were on a lower dosage than before the procedure.

Discussion

In the context of an ongoing randomized trial by our research group, we performed this first explorative study evaluating in detail the effect of TIF on reflux mechanisms and EGJ function. The major findings are that TIF reduced the number of postprandial TLESRs and the number and proximal extent of reflux episodes, which led to an improvement of acid exposure in the upright position after 6 months. Furthermore, EGJ distensibility was decreased, as measured directly after the endoscopic procedure.

Reduction in the number of TLESRs has been previously described in studies evaluating the mechanisms of conventional anti-reflux surgery, and this mechanism is thought to strongly contribute to the anti-reflux effect of conventional anti-reflux surgery [12, 13, 34]. In addition to the reduction in the number of TLESRs, we also observed a marked effect of TIF on the number and proximal extent of reflux episodes, during both the postprandial and the ambulatory measurement. This led to a significant improvement of acid exposure time in the upright position, but not in the supine position. This finding could be due to a different profile of reflux mechanisms in the two positions: in the upright position TLESRs are considered to be the dominant mechanism for reflux to occur, whereas in the supine position, especially during sleep or in the presence of hiatal hernia, other mechanisms could be of more importance [15, 35, 36]. TIF had a significant effect on the number of TLESRs, but may have a less distinct effect on the mechanisms causing reflux in the supine position.

The neurological pathways involved in the vago–vagal reflex that leads to a TLESR are well described; however, the mechanism by which fundoplication reduces the frequency of TLESRs remains to be determined [16, 37–39]. Several studies focusing on either the compliance of the proximal stomach [40–42] or on postoperative vagal nerve damage [41, 43, 44] have not been able to provide us with explanatory mechanisms. However, as shown in a recent study, localized distension of the EGJ itself increased the rate of TLESRs and was proposed as a potential mechanism for triggering of TLESRs [45]. The authors suggest a role for stretch- and tension receptors in the EGJ region that trigger TLESRs in response to distension. The reduction of EGJ distensibility by fundoplication gives rise to the hypothesis that fundoplication increases the threshold for triggering of TLESRs by reducing EGJ distensibility [46, 47]. In the present study, we observed a decrease in the number of TLESRs and a reduced EGJ distensibility after TIF, supporting the previously proposed hypothesis that the effect of TIF on the number of TLESRs may be due to the reduction of EGJ distensibility by the newly created fundic wrap. Further studies are needed to fully elucidate the mechanisms of fundoplication, especially the effect of the procedure on EGJ distensibility and the triggering of TLESRs, so that, in the future, surgeons are able to customize fundoplication in order to not only achieve a reduction in reflux events but also to prevent postoperative dysphagia and gas bloating.

The frequency of postprandial TLESRs in the present study is comparable to that of healthy subjects as described in early reports [31, 48, 49]. However, the proportion of TLESRs associated with liquid-containing reflux was higher in GERD patients, a finding in accordance with previous studies [18, 19]. In healthy subjects, the occurrence of reflux during TLESRs is limited due to a small opening of the EGJ, whereas in GERD patients, reflux of gastric juice can frequently occur during TLESRs due to loss of EGJ function [20, 21]. The goal of fundoplication is to restore normal EGJ function, restricting the occurrence of liquid-containing reflux during TLESRs, but allowing the occurrence of gas reflux. TIF was not able to reduce the proportion of TLESRs associated with liquid-containing reflux in the present study, in contrast with LARS [12, 13]. We hypothesize that the opening dimension of the EGJ during TLESRs remained large enough to allow the occurrence of liquid-containing reflux. Although we were not able to measure EGJ opening dimensions during TLESRs, we indeed observed no significant decrease in the CSA of the EGJ as measured with the EndoFLIP device after TIF.

During both postprandial and ambulatory measurements, we observed a marked effect of TIF on the number of liquid-containing reflux episodes; however, the number of gas reflux episodes were unaffected by TIF. TLESRs are the predominant mechanism for reflux to occur, but are also considered to be an essential mechanism for venting intragastric air by belching [16]. Conventional anti-reflux surgery can give rise to new gas-related symptoms by reducing TLESRs [50, 51]. TIF had no effect on gas reflux, as seen during both ambulatory and postprandial measurements. None of the patients participating in the present study developed any gas-related symptoms after the procedure, and earlier studies with more participants reported no gas bloating in patients after TIF [9, 52].

Furthermore, the present study showed that TIF reduces both the number and the percentage of proximal reflux episodes; this finding was also reported in GERD patients after Nissen fundoplication [13]. The proximal extent of the refluxate is thought to be related to the volume of the refluxate and to contribute to symptom perception [53–56]. We speculate that the observed reduction in EGJ distensibility after TIF may result in a reduction of the volume of the refluxate, thereby reducing symptom perception.

The present study was neither primarily designed nor powered to assess the clinical efficacy of TIF, but we observed an improvement in symptom scores as measured with the GERD-HRQL, in PPI use and in acid exposure time in the upright position. Long-term data from an ongoing randomized trial by our research group comparing TIF with PPI therapy in GERD patients are awaited to fully assess the anti-reflux effect of the procedure.

In summary, we aimed to explore the mechanisms underlying the anti-reflux effect of TIF. The procedure significantly reduced the number of TLESRs and the number of TLESRs associated with liquid-containing reflux. This effect may be due to the observed reduction of EGJ distensibility, raising the threshold for triggering TLESRs. This resulted in a reduction of the number of liquid-containing reflux episodes and improvement in esophageal acid exposure in the upright position. However, the anti-reflux effect of TIF showed to be selective for liquid-containing reflux, thereby maintaining the ability of venting gastric air. Further randomized controlled trials are required to assess the anti-reflux effect and long-term efficacy of TIF.

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